FRASER HEALTH LONGTERM CARE ROUNDS

APRIL 19, 2023

APPROACH TO COMMON HEMATOLOGIC CONDITIONS

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RCH HEMATOLOGY

DISCLOSURE

- I **do not** have an affiliation (financial or otherwise) with any for-profit or not-for-profit organizations

OBJECTIVES

- Review approach to and management of:
  - Venous Thrombosis
  - Anemia
  - ~~Thrombocytopenia~~

CASE 1

- 82yo Tom Bossi moved to LTC 6 months ago due to dementia
- Supportive family with POA.
- Mobile not requiring walking aid
- PMHx: HTN, DM, mild CKD eGFR 50s
- Meds: Amlodipine, Ramipril, metformin
- New onset of left leg swelling and pain. No recent trauma. No recent illness. No shortness of breath
- On exam: Vitals stable. Left calf swollen (>3 cm larger compared to the right) and red, minor tenderness on palpation. No systemic symptoms including chills, fever.

IS THIS DVT?

Well's criteria for DVT

Table 1. Clinical Model for Predicting the Pretest Probability of Deep-Vein Thrombosis.*

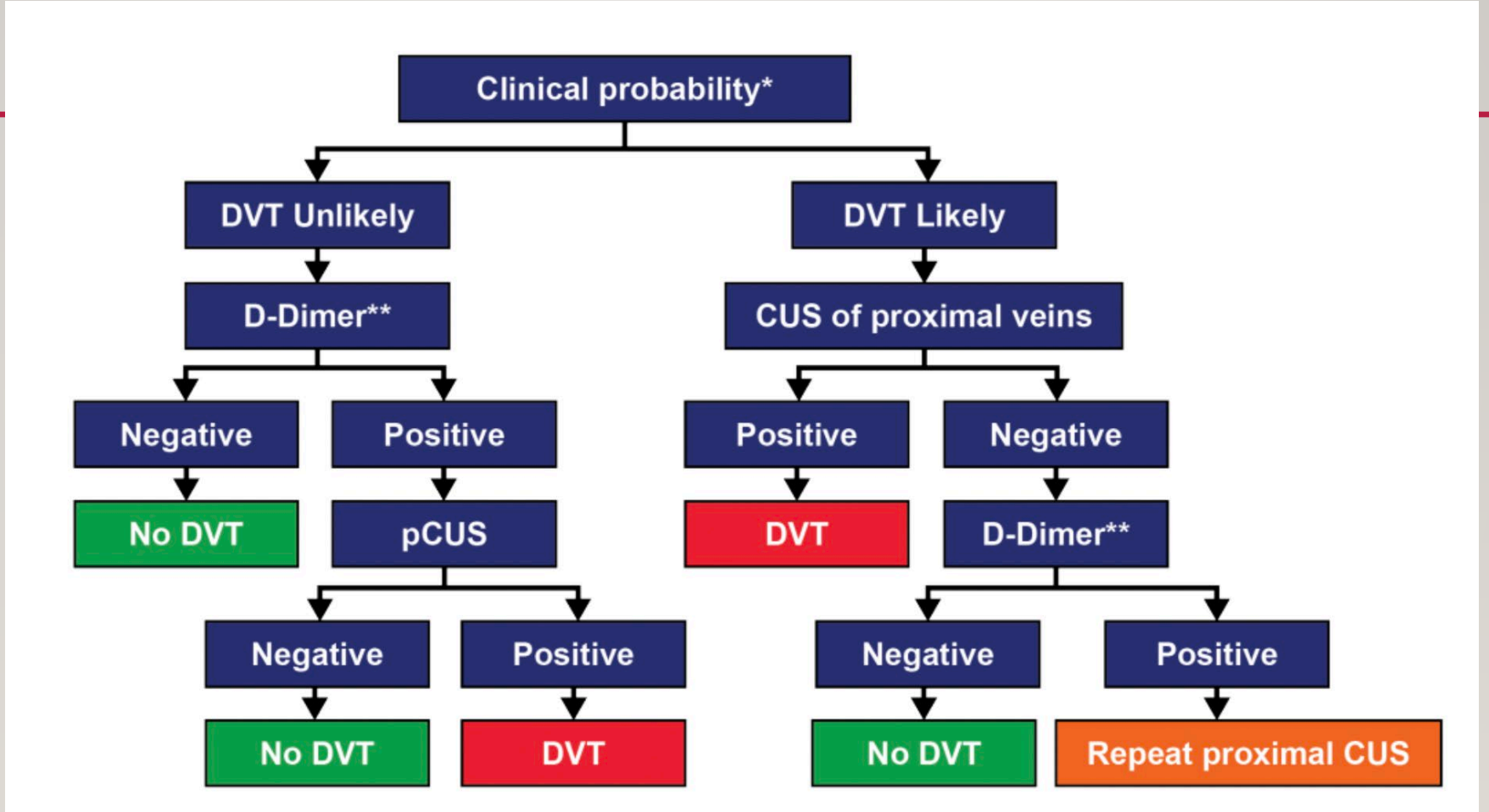
Clinical Characteristic	Score
Active cancer (patient receiving treatment for cancer within the previous 6 mo or currently receiving palliative treatment)	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recently bedridden for 3 days or more, or major surgery within the previous 12 wk requiring general or regional anesthesia	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling at least 3 cm larger than that on the asymptomatic side (measured 10 cm below tibial tuberosity)	1
Pitting edema confined to the symptomatic leg	1
Collateral superficial veins (nonvaricose)	1
Previously documented deep-vein thrombosis	1
Alternative diagnosis at least as likely as deep-vein thrombosis	−2

* A score of two or higher indicates that the probability of deep-vein thrombosis is likely; a score of less than two indicates that the probability of deep-vein thrombosis is unlikely. In patients with symptoms in both legs, the more symptomatic leg is used.

Wells P et al. NEJM 2003. 349:1227

Score of 1, probability of DVT 6%
Score of ≥ 2, probability 28%

Thrombosis Canada
Thrombose Canada



CASE

- You were lucky and able to arrange urgent ultrasound doppler next day
- Patient has low risk of bleeding, so you decided to start empiric anticoagulation.

ANTICOAGULATION THERAPY

- Direct oral anticoagulants (DOACs) are preferred over warfarin (Chest Guidelines 2021)
- Warfarin, Edoxaban, Dabigatran all require initial bridging LMWH
- DOACs are generally ok to use even in patients with cancer
  - Avoid if upper GI cancer
  - Avoid in extreme weight <45 kg or >140 kg

Stevens SM et al. Chest Guidelines for VTE 2021

DOACS

	Apixaban	Rivaroxaban
Dosage	10 mg bid x 1 week then 5 mg bid	15 mg bid x 3 weeks then 20 mg daily with food
CKD	Safe if GFR >25, use with caution if GFR 15-30	Avoid use if GFR <30
Drug interaction	Avoid use with inducers of CYP3A4 and P-glycoprotein, eg Carbamazepine, Dilantin, rifampin, ketoconazole, anti-virals such as paxlovid, tenofovir	
GI Absorption	Mainly absorbed in distal small bowel and colon. Not preferred if previous colectomy	Release dependent on passage through stomach. Avoid if previous gastric bypass or gastrectomy
Coverage	Generic, no SAR required	Needs SAR (cost approx. $3/day)

Hakeam H, Al-Sanea N. J Thromb Thrombolysis 2017; 43:343

WHICH DOAC?

- Randomized prospective trial comparing bleeding risk between Rivaroxaban and Apixaban in treatment of VTE (COBRRA) is underway with completion date expected end of 2023.
- Meta-analysis of phase III trials suggests Apixaban is associated with lower risk of bleeding compared to other DOACs (Mantha S, Ansell J. J Thromb Thrombolysis 2015; 39:155)

Table 5 Estimated relative risk of selected outcomes for the six possible pairwise comparisons of novel oral anticoagulants

	Apixaban versus Dabigatran			Apixaban versus Rivaroxaban			Apixaban versus Edoxaban			Rivaroxaban versus Dabigatran			Rivaroxaban versus Edoxaban			Edoxaban versus Dabigatran		
	RR	95 % CI	*p*	RR	95 % CI	*p*	RR	95 % CI	*p*	RR	95 % CI	*p*	RR	95 % CI	*p*	RR	95 % CI	*p*
Recurrent VTE	0.77	0.47–1.27	0.30	0.94	0.60–1.48	0.80	0.94	0.62–1.43	0.78	0.82	0.51–1.30	0.40	1.00	0.68–1.46	>0.99	0.82	0.53–1.26	0.36
Major bleeding	0.42	0.21–0.87	0.02	0.57	0.29–1.15	0.12	0.37	0.19–0.73	<0.001	0.74	0.42–1.30	0.30	0.64	0.38–1.08	0.10	1.15	0.66–2.00	0.62
Major or clinically relevant nonmajor bleeding	0.71	0.53–0.96	0.02	0.47	0.37–0.61	<0.001	0.54	0.42–0.70	<0.001	1.50	1.17–1.92	0.001	1.15	0.95–1.39	0.16	1.31	1.02–1.68	0.04
Death	0.79	0.45–1.40	0.42	0.88	0.54–1.45	0.63	0.75	0.47–1.21	0.24	0.89	0.54–1.46	0.65	0.85	0.58–1.24	0.40	1.05	0.65–1.69	0.84

RR relative risk, *CI* confidence interval, *VTE* venous thromboembolism

RIVAROXABAN VS APIXABAN

- Retrospective cohort study on patients newly started on rivaroxaban or apixaban for treatment of VTE. Median follow up ~100 days

Table 2. Risk for Recurrent VTE and Bleeding Comparing Apixaban and Rivaroxaban in Patients With VTE*

Outcome	Apixaban				Rivaroxaban				Adjusted Marginal HR (95% CI)
	Patients, n	Events, *n*	PYs of Follow-up	Incidence Rate per 100 PYs	*Patients, n*	Events, *n*	PYs of Follow-up	Incidence Rate per 100 PYs	
Recurrent VTE	18 618	475	5314	8.9	18 618	595	5200	11.4	0.77 (0.69–0.87)
DVT	–	442	5322	8.3	–	501	5223	9.6	0.85 (0.74–0.97)
PE	–	33	5382	0.6	–	94	5276	1.8	0.59 (0.39–0.91)
Bleeding	18 618	386	5344	7.2	18 618	577	5239	11.0	0.60 (0.53–0.69)
GI	–	382	5344	7.0	–	566	5240	10.6	0.60 (0.53–0.69)
Intracranial	–	4	5389	0.2	–	11	5298	0.4	0.54 (0.14–1.20)

Dawwas GK et al. Annals of Int Med 2022; 175:20

NON DOAC TREATMENT

- Extreme weight or major drug interaction:
  - Start LMWH and transition to warfarin
  - Needs overlap of both for 5 days until INR therapeutic for 2 days (target 2.5, range 2.0-3.0)
  - Local ER OPAT may be able to help with transition and with daily injections
- eGFR <25:
  - Renal dosing of Enoxaparin 1mg/kg SC daily and transition to warfarin
  - Or Tinzaparin 175 mg/kg SC daily and transition to warfarin
- Active upper GI cancer or intolerant of PO medication:
  - Start LMWH with either Enoxaparin 1.5 mg/kg SC daily or Dalteparin 200 units/kg SC daily
  - Can get SAR for 3 months when treating cancer associated thrombosis

WHAT WORK UP SHOULD BE DONE?

- CBC, creatinine, liver enzymes
- D-dimer
- INR, PTT if bloodwork can be done prior to starting anticoagulation
- Consider age appropriate cancer screen
- Consider CXR if no recent chest imaging

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 20, 2015 VOL. 373 NO. 8

Screening for Occult Cancer in Unprovoked Venous Thromboembolism

Marc Carrier, M.D., Alejandro Lazo-Langner, M.D., Sudeep Shivakumar, M.D., Vicky Tagalakis, M.D., Ryan Zarychanski, M.D., Susan Solymoss, M.D., Nathalie Routhier, M.D., James Douketis, M.D., Kim Danovitch, C.C.R.P., Agnes Y. Lee, M.D., Gregoire Le Gal, M.D., Philip S. Wells, M.D., Daniel J. Corsi, Ph.D., Timothy Ramsay, Ph.D., Doug Coyle, Ph.D., Isabelle Chagnon, M.D., Zahra Kassam, M.D., Hardy Tao, M.D., and Marc A. Rodger, M.D., for the SOME Investigators*

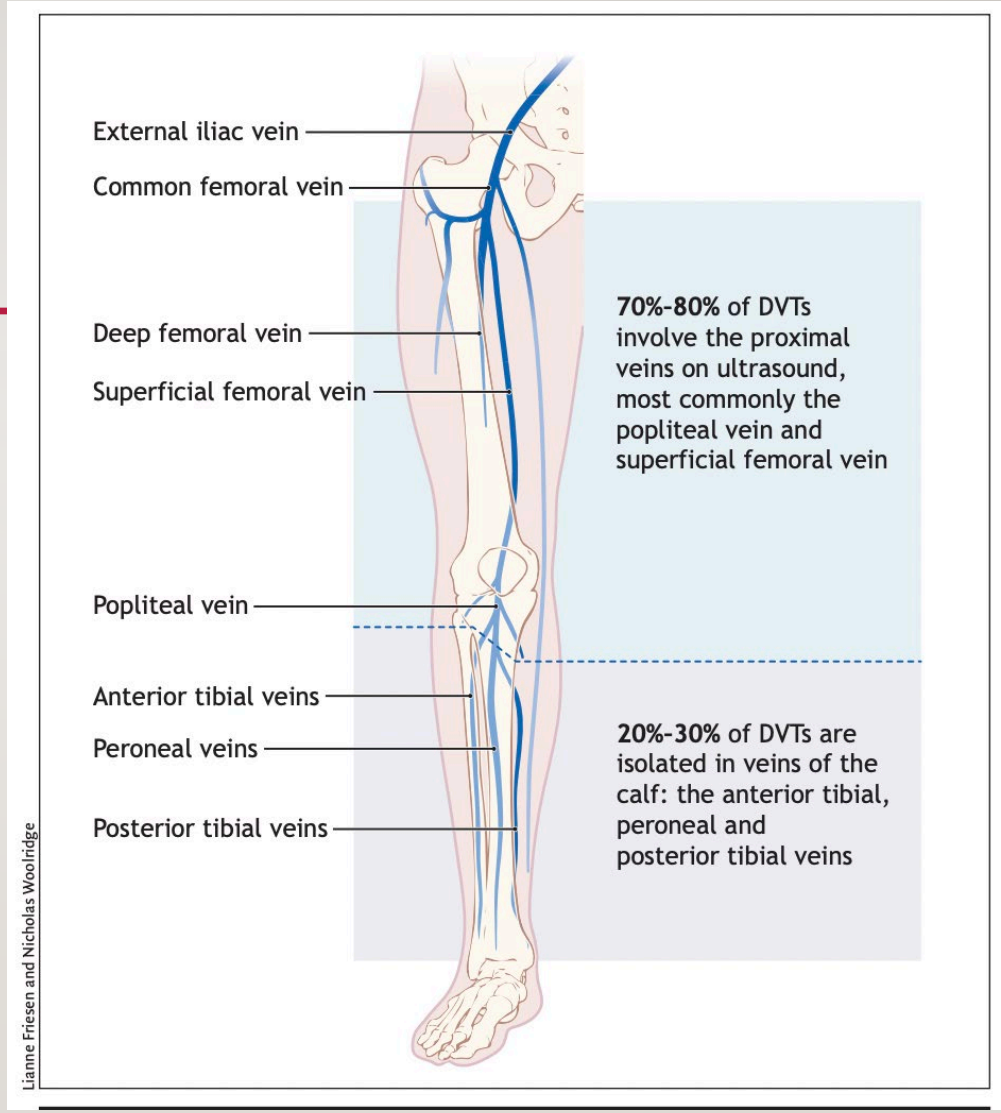
Patients assigned to the limited screening strategy underwent a complete history taking and physical examination, measurement of complete blood counts and serum electrolyte and creatinine levels, liver-function testing, and chest radiography. On the basis of recommendations by the Canadian Task Force on Preventive Health Care[12] and the U.S. Preventive Services Task Force,[13] sex-specific screening was conducted if it had not been performed in the previous year. A breast examination, mammography, or both were performed in women older than 50 years of age, and Papanicolaou (Pap) testing and a pelvic examination were performed in women 18 to 70 years of age who had ever been sexually active. A prostate examination, prostate-specific antigen test, or both were performed in men older than 40 years of age.

+/- CT abd/pelvis

- There was no significant difference between the two study groups in the mean time to a cancer diagnosis (4.2 months in the limited-screening group and 4.0 months in the limited-screening-plus-CT group, P=0.88) or in cancer-related mortality (1.4% and 0.9%, P=0.75).
- Routine screening with CT of the abdomen and pelvis did not provide a clinically significant benefit.

CASE

- He was started on Apixaban 10 mg bid
- His bloodwork came back unremarkable, eGFR 50. Chest X-ray normal. PSA normal. Stool FIT neg. No iron deficiency.
- Ultrasound next day confirms left leg DVT involving popliteal vein and posterior tibial vein



Scarvelis D and Wells P. CMAJ 2006. 175:1088

TREATMENT OF DISTAL DVT

- Distal DVT
  - Definition: posterior tibial, anterior tibial, peroneal vein, gastronemius vein
  - If symptomatic, clot >5 cm or close to popliteal vein, has ongoing risk factor for blood clot extension or unable to return for repeat imaging → 3 months of AC recommended
  - If minimally symptomatic and potential high risk of bleed → serial ultrasound (weekly x 2) and only anticoagulate if proximal extension of clot (10-15% risk)

TREATMENT OF SUPERFICIAL VENOUS THROMBOSIS

- Superficial venous thrombosis
  - Definition: greater saphenous, lesser saphenous veins
  - Concomitant DVT → treat as DVT
  - Isolated SVT that extends to within 3 cm of saphenofemoral junction (SFJ) or saphenopopliteal junction (SPJ) ➔ treat with 3 months of AC
  - Isolated SVT ≥ 5 cm in length located > 3 cm from SFJ/SPJ → 45 days of Xarelto 10 mg or fondaparinux 2.5 mg SC or prophylaxis LMWH SC
  - Isolated SVT < 5cm in length and located >3 cm from SFJ/SPJ → oral or topical NSAIDS, warm or cool compress

REFERRAL TO HEMATOLOGY/THROMBOSIS CLINIC

- Hematologists at:
  - BH
  - RCH (covers Burnaby, New Westminster, Port Moody, Coquitlam, Port Coquitlam, Maple Ridge, Pitt Meadows)
  - SMH (covers Surrey, Delta, Langley, White Rock, Abbotsford, Chilliwack)
- Some internists at Abbotsford and Surrey also see thrombosis patients
- Anticoagulation Clinic at SMH and RCH/ERH/RMH ER OPAT can help with LMWH injections and transition to warfarin (does not include assessment by heme)

CASE 1

- He tolerated Apixaban well with resolution of his leg symptoms after 2-3 weeks
- He has now completed 3 months of Apixaban
- Follow up ultrasound showed minimal thickening of the popliteal vein consistent with residual clot

- How long should he be treated for his unprovoked DVT?

DURATION OF TREATMENT

- 3 months minimum duration for acute VTE in all patients. Risk of recurrence doubles if duration shortens to 4-6 weeks (Thrombosis Canada)
- Duration of anticoagulation depends on risk of VTE recurrence and bleeding risk

	Major Risk factor	Minor Risk Factor	Unprovoked
Definition	OR ≥ 30 min or bedrest ≥ 3 days	OR < 30 min, bed rest <3 days	No modifiable risk factor
Risk of recurrence at 1 year	1%	5%	10%
Risk of recurrence at 5 years	3%	15%	25-30%

- Average risk of major bleeding on DOAC estimated at 0.8% / year

Rodger M, Gal G. Blood Advances 2018; 21: 3081

BLEEDING RISK ASSESSMENT

- Extensively validated bleeding scores such as ACCP, HAS-BLED, RIETE all have limitations: majority of patients on VKA instead of DOAC, Afib as reason for AC rather than VTE, assessment done in acute treatment for VTE
- Risk of bleeding with warfarin is higher than DOACs
- Risk of anticoagulant-induced bleeding is highest during the first 3 months of treatment and stabilizes after the first year.
- There is no validated tools to predict bleeding risk in patients on long term DOAC for VTE and identify those who will not benefit from ongoing AC.

Klok FA, Huisman MV. Blood 2020; 135:724.

BLEEDING RISK ASSESSMENT

- These bleeding scores however can help identify any modifiable risk factors to minimize risk of bleeding:
  - Good control of blood pressure
  - Maintain kidney function
  - Assess need for concomitant anti-platelet therapy
  - Avoid NSAIDs or supplements with blood thinning effect
- Assessment further complicated by heterogenous fatality/ morbidity rate with bleeding vs recurrent thrombosis
- Some experts estimate annual bleeding risk >3% may outweigh the benefit of long term anticoagulation but this remains controversial

Table I. The VTE-BLEED score with original definition of variables (Klok *et al*, 2016). Eur Resp Journal 48:1369

Factor	Score
Active cancer*	2
Male with uncontrolled arterial hypertension† (≥140 mmHg)	1
Anaemia‡ (Hb <130 in men, <120 in women)	1·5
History of bleeding§	1·5
Age ≥60 years old	1·5
Renal dysfunction¶ (< 60 ml/min)	1·5
Classification of patients with the VTE-BLEED score	
Low bleeding risk	Total score <2
High bleeding risk	Total score ≥2

Rodger M, Gal G. Blood Advances 2018; 21: 3081

HOW ABOUT D-DIMER OR FOLLOW UP IMAGING?

- Multiple tools designed to further risk stratify patients with unprovoked VTE and recurrent risk of thrombosis, eg HERDOO2, DASH, Vienna, DULCIS
- Normal D-dimer after stopping anticoagulant is associated with lower risk of recurrence. However, there are other factors such as gender, age that need to be considered
- Therefore, D-dimer alone should not be used to make decision on whether to stop anticoagulation.
- Follow up imaging is helpful to establish new baseline for future reference. However, presence or absence of residual clot should not be a determinant on duration of therapy

CASE 1

- He was kept on Apixaban 5 mg bid given good tolerance.
- Intermittent assessment of blood pressure, CBC, liver and kidney function and monitoring of bleeding

- 9 months after his diagnosis of DVT, he starts to develop recurrent minor epistaxis lasting 10-15 minutes
  - CBC showed normal Hb and platelet, creatinine stable

MANAGEMENT OF BLEED

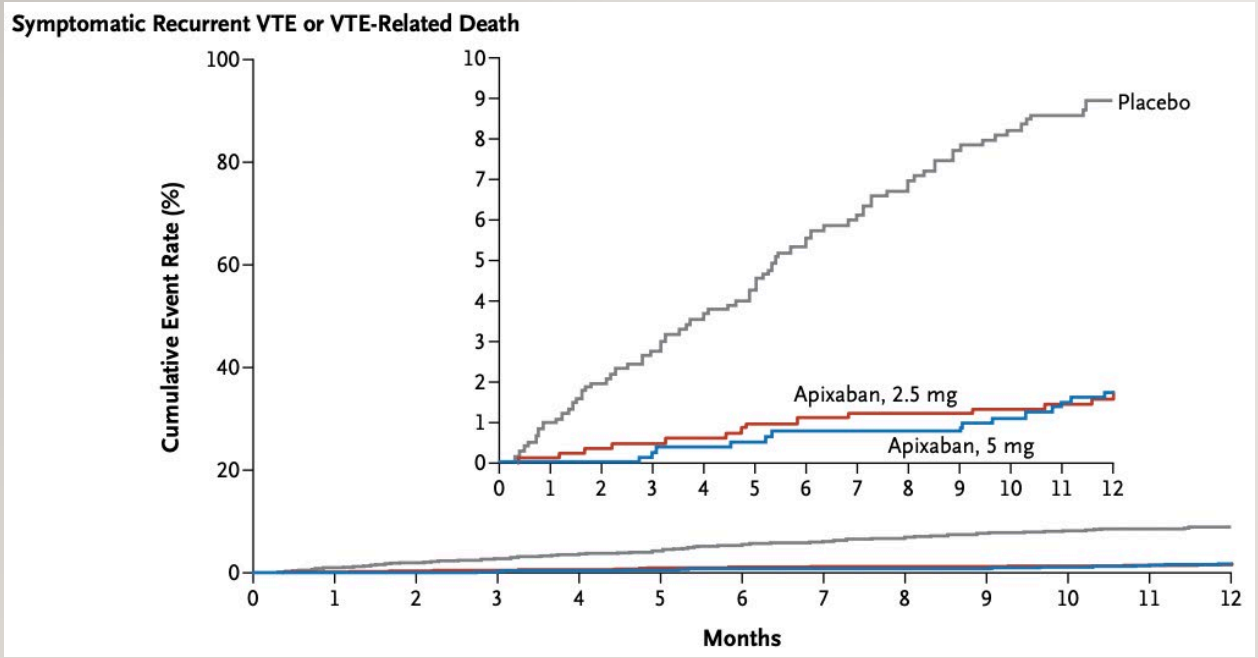
- Minor bleed/bruising → continue AC and try local measures to minimize recurrent bleed
- Recurrent minor bleed → hold AC x 24-48 hr and try local measures.
  - Check CBC, creatinine (INR if on warfarin)
  - Review medications/supplements
  - Re-challenge after bleeding settles.
  - Low threshold to hold AC for short term if VTE occurred > 6-12 months ago
- Moderate/Severe bleed → stop AC and send to ER for assessment

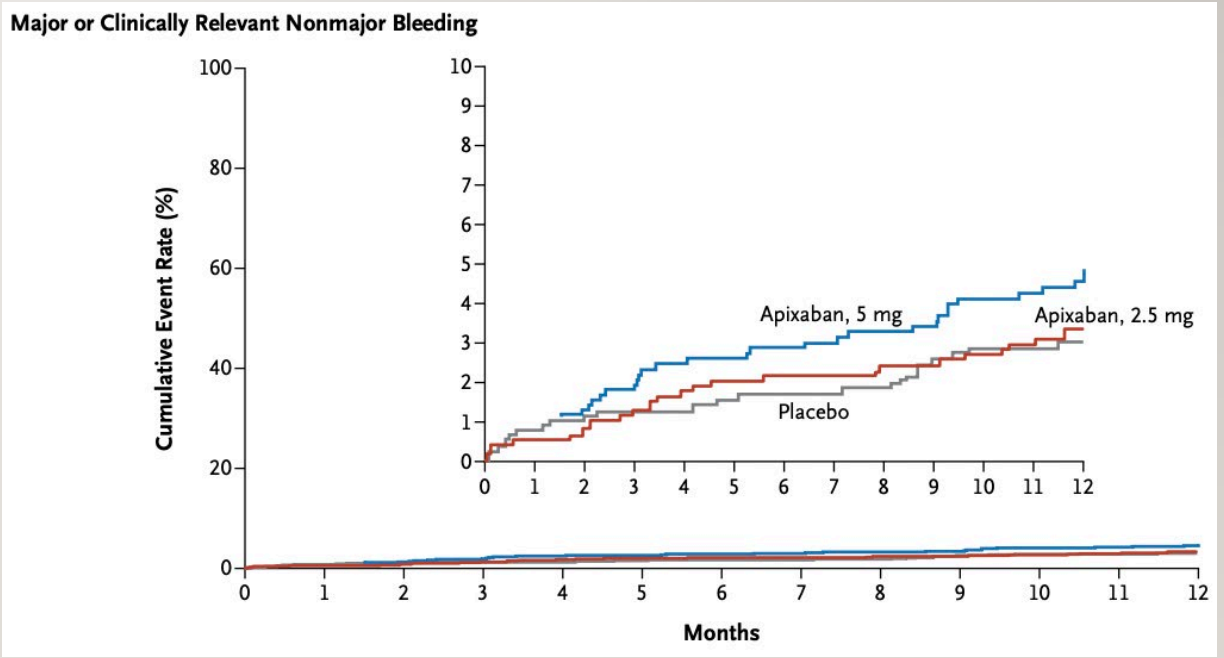
CASE 1

- Recurrent minor epistaxis persists
- Assessed by ENT and no visible vessel to cauterize.
- Trial of mucosal moisturization with Vaseline did not make difference
- After discussion of risk and benefit of ongoing anticoagulation and risk of recurrent thrombosis with family, he was stepped down to Apixaban 2.5 mg bid with resolution of nosebleed

LONG TERM APIXABAN

AMPLIFY EXTEND study

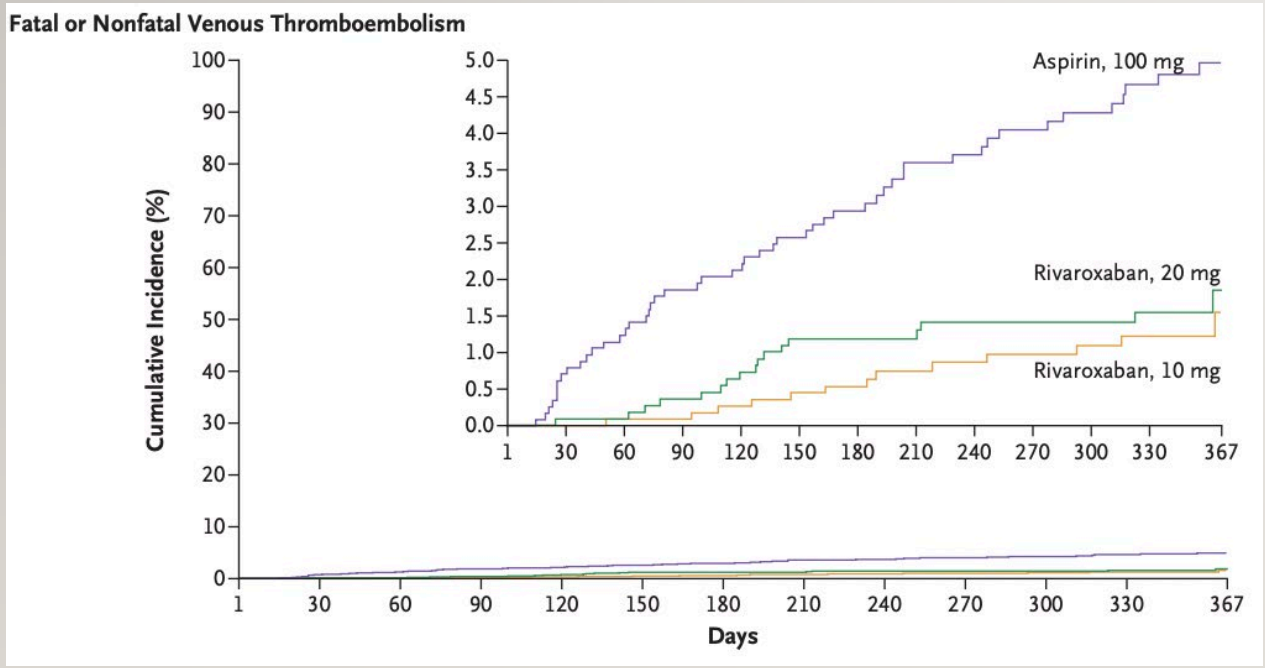


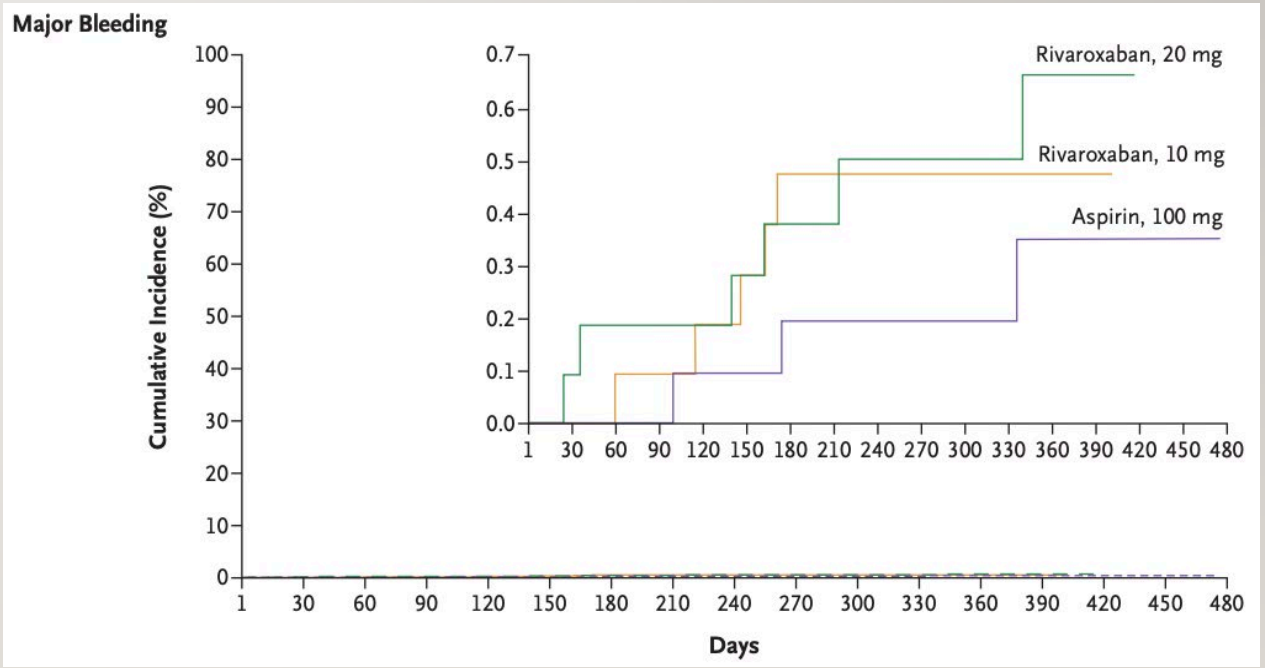


Agnelli G el al. NEJM 2013;368:699

RIVAROXABAN DOSAGE

EINSTEIN CHOICE study





Weitz JI et al. NEJM 2017; 376:1211

WHAT I DO….

- I consider empiric step down to low dose DOAC if:
  - one episode of unprovoked VTE with small/moderate clot burden
  - After 6 months of full dose AC
  - "high risk of bleeding" – frail, history of fall, CKD
- Or if bleeding issue on full dose anticoagulation

- Ongoing RENOVE trial will hopefully provide more concrete data on low dose vs full dose Apixaban/Rivaroxaban after unprovoked VTE

PERI-PROCEDURE ANTICOAGULATION MANAGEMENT

Chest guideline

Lower Mainland IR guideline

Thrombosis Canada

Perioperative Management of Antithrombotic Therapy

An American College of Chest Physicians Clinical Practice Guideline

James D. Douketis, MD, FCCP; Alex C. Spyropoulos, MD, FCCP; M. Hassan Murad, MD, MPH; Juan I. Arcelus, MD; William E. Dager, PharmD; Andrew S. Dunn, MD, MPH; Ramiz A. Fargo, MD, FCCP; Jerrold H. Levy, MD; C. Marc Samama, MD; Sahrish H. Shah, MBBS; Matthew W. Sherwood, MD; Alfonso J. Tafur, MD; Liang V. Tang, MD; and Lisa K. Moores, MD, FCCP

Skipping or delaying the immediate pre-procedure dose

Douketis JD et al. Chest 2022; 162:E207

TABLE 2] Suggested Risk Stratification for Procedural Bleed Risk, Based on ISTH Guidance Statements[25]

High-bleed-risk surgery/procedure[a] (30-d risk of major bleed ≥ 2%)	Major surgery with extensive tissue injury Cancer surgery, especially solid tumor resection (lung, esophagus, gastric, colon, hepatobiliary, pancreatic) Major orthopedic surgery, including shoulder replacement surgery Reconstructive plastic surgery Major thoracic surgery Urologic or GI surgery, especially anastomosis surgery Transurethral prostate resection, bladder resection, or tumor ablation Nephrectomy, kidney biopsy Colonic polyp resection Bowel resection Percutaneous endoscopic gastrostomy placement, endoscopic retrograde cholangiopancreatography Surgery in highly vascular organs (kidneys, liver, spleen) Cardiac, intracranial, or spinal surgery Any major operation (procedure duration > 45 min) Neuraxial anesthesia[b] Epidural injections
Low-to-moderate-bleed-risk surgery/procedure[c] (30-d risk of major bleed 0%-2%)	Arthroscopy Cutaneous/lymph node biopsies Foot/hand surgery Coronary angiography[d] GI endoscopy ± biopsy Colonoscopy ± biopsy Abdominal hysterectomy Laparoscopic cholecystectomy Abdominal hernia repair Hemorrhoidal surgery Bronchoscopy ± biopsy
Minimal-bleed-risk surgery/procedure[e] (30-d risk of major bleed approximately 0%)	Minor dermatologic procedures (excision of basal and squamous cell skin cancers, actinic keratoses, and premalignant or cancerous skin nevi) Ophthalmologic (cataract) procedures Minor dental procedures (dental extractions, restorations, prosthetics, endodontics), dental cleanings, fillings Pacemaker or cardioverter-defibrillator device implantation

PERI-PROCEDURE MANAGEMENT

	Apixaban	Rivaroxaban	Dabigatran	Edoxaban	LMWH
Low to mod risk	1 day off	1 day off	1 day if CrCl ≥ 50 2 days if CrCl < 50	1 day off	Half dose ~24 hr prior to OR
High risk	2 days off	2 days off	2 days if CrCl ≥ 50 4 days if CrCl <50	2 days off	Half dose ~24 hr prior to OR

- Bridging LMWH is NOT required during interruption of DOAC
- Post procedure if no bleeding complication, DOAC can be resumed >24 hr after low-mod risk bleeding procedures and 48-72 hours after high risk bleeding procedures
- Patients with high risk of recurrent VTE, consider starting prophylactic LMWH 12-24 hr after procedure

Douketis JD et al. Chest 2022; 162:E207

LOWER MAINLAND IR GUIDELINES

http://shop.healthcarebc.ca/MedicalImaging/ABCD-21-07-90001.pdf

HIGH RISK PROCEDURES

HIGH RISK INR ≤ 1.8 or ≤ 2.5 with chronic liver disease Target INR for warfarin reversal: ≤ 1.5 Platelets > 50 x 10^9/L Testing within 2 weeks for outpatient	Anticoagulant / Antiplatelet MEDS	Discontinue Yes*/ No	Suggested Timing of LAST dose BEFORE procedure*	Timing of FIRST dose AFTER day of procedure*
VASCULAR ▪ TIPS ▪ Catheter-directed thrombolysis ▪ Arterial interventions >6Fr access **NON-VASCULAR** **Abdominal Procedures** ▪ Solid organ, lung and deep tissue biopsies ▪ Prostate biopsy ▪ Deep abscess drainage ▪ PCNL/Nephrostomy ▪ G and GJ-tube placement ▪ Biliary drainage (PTBD) ▪ Thermal ablations – liver, kidney, lung, MSK **High Risk Spine & Neurological Procedures** ▪ Vertebroplasty ▪ Kyphoplasty ▪ Cervical spine facet blocks ▪ Epidural injection (lumbar/thoracic/cervical) NOTE: Specialized Neurovascular Procedures are excluded, including carotid stenting, and intra-cranial embolization	▪ aspirin (ASA), low dose (81 mg)	Yes	- 5 days	Day + 1
	▪ clopidogrel (Plavix®) ▪ aspirin, non-low dose ▪ ticagrelor (Brilinta®)	Yes	- 5 days†	Day + 1 or + 2
	▪ prasurgrel (Effient®)	Yes	- 7 days†	Day + 1 or + 2
	▪ NSAIDs	Yes	NA	NA
	▪ warfarin (Coumadin®)	Yes	- 5 days, CHECK INR, TARGET ≤ 1.5 *consider bridging in high thrombosis risk cases	Day + 1
	▪ subcutaneous heparin (prophylactic)	Yes	- 8 hrs prior	Day 0 (evening)
	▪ low molecular weight heparin (LMWH)	Yes	prophylactic: > 12 hrs prior therapeutic: > 24 hrs prior	Day 0 (evening)
	▪ (IV) unfractionated heparin	Yes	infusion to stop 4 hrs prior	8 hrs after
	▪ dabigatran (Pradaxa®)	Yes	GFR >50: - 3 days	Day + 2 or + 3
	▪ rivaroxaban (Xarelto®) ▪ apixaban (Eliquis®) ▪ edoxaban (Lixiana®)	Yes	Withhold 2 doses if CrCl ≥ 50 mL/min Withhold 3 doses if CrCl < 50 mL/min	Day + 2 or + 3
	▪ fondaparinux (Arixtra®)	Yes	-3 days for CrCl ≥ 50 mL/min -5 days for CrCl < 50 mL/min	Day + 1 Day + 2 or + 3

LOW RISK PROCEDURES

LOW RISK No routine pre-procedural INR/CBC unless bleeding diathesis suspected; then consider INR ≤ 3.0 and Platelets > 20 x 10^9/L. For chronic liver disease, INR is not required.	Anticoagulant / Antiplatelet MEDS	Discontinue Yes*/ No	Suggested Timing of LAST dose BEFORE procedure if discontinuing	Timing of FIRST dose AFTER day of procedure*
VASCULAR ▪ Dialysis access and venous interventions including varicocele embolization, venography ▪ IVC filter placement/removal ▪ PICC insertion ▪ Uncomplicated catheter/line exchange/removal ▪ Angiography/arterial intervention up to 6 Fr access (eg. UAE) ▪ Transjugular liver biopsy ▪ Tunneled CVC/Port/Hickman **NON-VASCULAR** ▪ Catheter exchange or removal (GU, biliary, abscess) ▪ Superficial abscess drainage ▪ Core biopsy – breast, extremity or other superficial location ▪ Joint injection or aspiration, including facet joint, nerve root /medial branch ▪ GI tract stenting (colon, esophagus) ▪ Hysterosalpingography, Fallopian Tube Recanalization ▪ Non-tunneled chest tube ▪ Lumbar puncture and Epidural injections (21 G or smaller) **Exception:** Thoracentesis or paracentesis can be carried out with any platelet count or INR **Superficial Aspiration / Biopsy (FNAB)** **Breast, Extremities, Lymph nodes, Thyroid** NOTE: Most LOW risk procedures do not require the discontinuation of anticoagulation/antiplatelet therapy.	▪ aspirin (ASA), any dose	No		
	▪ clopidogrel (Plavix®) ▪ ticagrelor (Brilinta®)	Possible to continue	Do not withhold	
	▪ prasurgrel (Effient®)	Possible to continue	Do not withhold	
	▪ warfarin (Coumadin®)	Possible to continue	- 5 days, TARGET INR ≤ 3.0, *consider bridging in high thrombosis risk cases	Day 0 (evening)
	▪ subcutaneous heparin ▪ low molecular weight heparin (LMWH) – prophylactic	No		
	▪ low molecular weight heparin (LMWH) – therapeutic	Possible to continue	Do not withhold	
	▪ (IV) unfractionated heparin	Possible to continue	Do not withhold	
	▪ dabigatran (Pradaxa®)	Possible to continue	Do not withhold	
	▪ rivaroxaban (Xarelto®) ▪ apixaban (Eliquis®) ▪ edoxaban (Lixiana®)	Possible to continue	Do not withhold	
	▪ fondaparinux (Arixtra®)	Possible to continue	Do not withhold	

Thrombosis Canada

Thrombose Canada

www.thrombosiscanada.ca

TOOLS

Algorithms

- Anticoagulant Dosing In Atrial Fibrillation
- Perioperative Anticoagulant Management Algorithm
- Thrombophilia Testing Algorithm
- Diagnosing and Ruling Out VIPIT/VITT

Acute Management Algorithms

- Atrial Fibrillation
- Bleed Management
- Deep Vein Thrombosis
- Pulmonary Embolism

Checklists

- DOAC Follow-up

Perioperative Anticoagulant Management Algorithm

Procedural Bleeding Risk

○ Low (minor non-dental procedure)

- Cataract surgery
- Dermatologic procedures (e.g. biopsy)
- Gastroscopy or colonoscopy without biopsies
- Coronary angiography
- Permanent pacemaker insertion or internal defibrillator placement (if bridging anticoagulation is not used)
- Selected procedures (e.g. thoracentesis, paracentesis, arthrocentesis)

○ Low (minor dental procedure)

○ Moderate

○ High

< Back

CASE 2

- 79yo Annie Mia in LTC for past year
- PMHx: HTN, Afib, CAD, CHF, CKD baseline Cr 105 (GFR 45), RA, Iron deficiency
- Med: Apixaban, ASA, bisoprolol, ramipril, Lipitor, prednisone 5 mg, PO Fe
- Several week history of increasing joint discomfort
- Family noted her to be more fatigue and pale
- No visible bleeding, no symptoms of infection. Appetite is good. No constitutional symptoms

CASE 2 BLOODWORK

- Hb 95, MCV 80, WBC 5.6 with normal differentials, platelet count 164. (Previous CBC from 6 months ago Hb 115, MCV 85, WBC 7.0, platelet 148)
- Creatinine 126, eGFR 35 ml/min
- ALT 36
- Ferritin 65, Vitamin B12 367
- TSH 2.35
- CRP 60

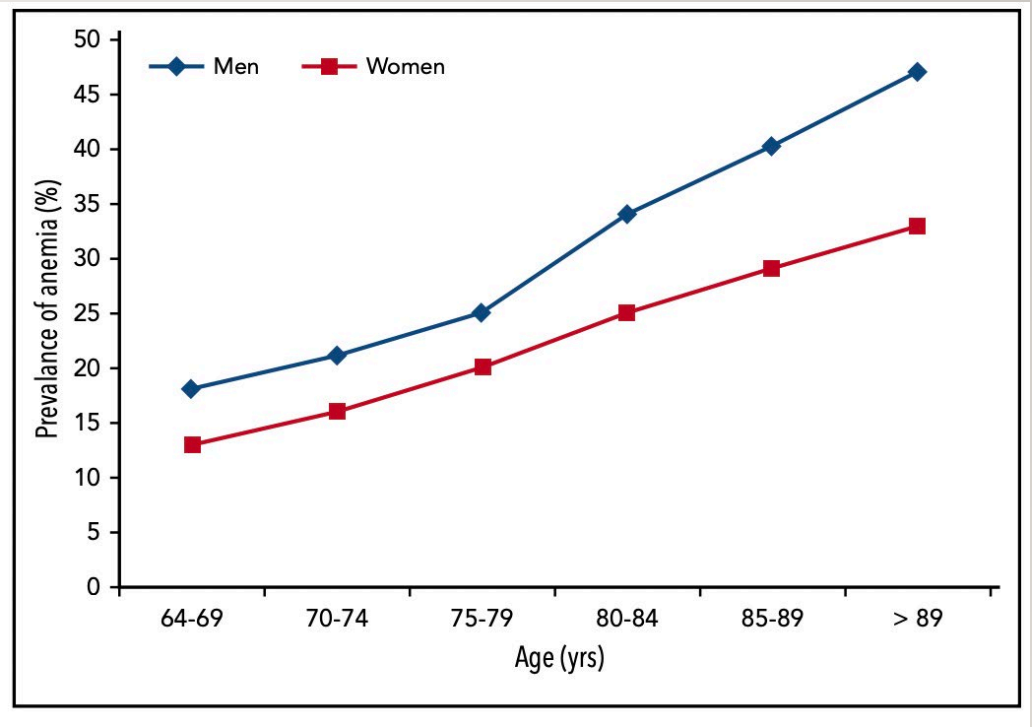
Worsened GFR may contribute to anemia

Iron deficient

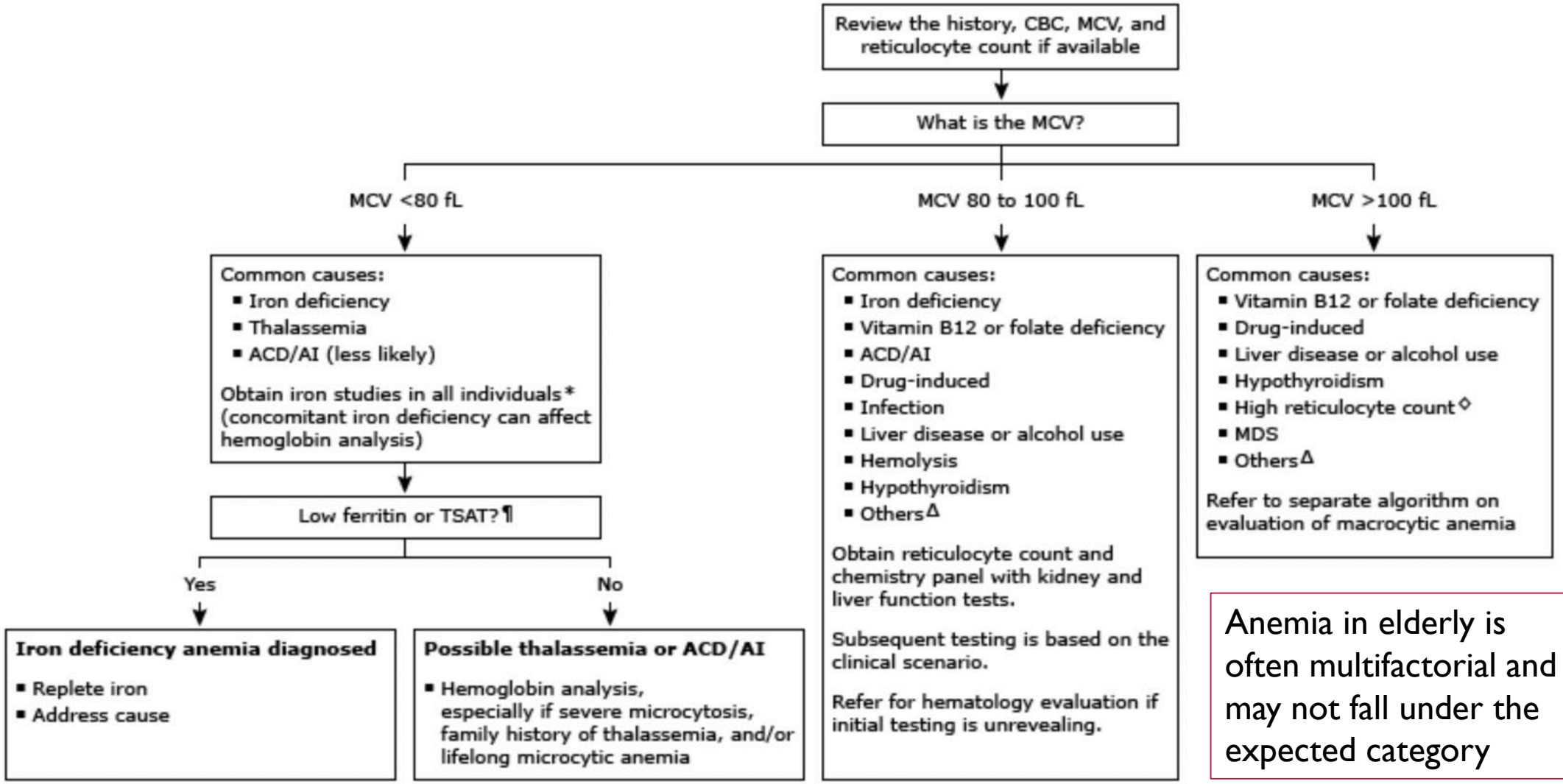
Active inflammation likely from arthritis flare

ANEMIA IN ELDERLY

- Defined by WHO as Hb <130 in men and <120 in women
- Anemia is a risk factor for CV disease, cognitive impairment, insomnia, impaired mood, restricted QoL.
- Anemia is associated with reduced executive function and physical performance
- Also associates with increased risk of falls and fractures



Stauder R et al. Blood 2018; 131:505



Anemia in elderly is often multifactorial and may not fall under the expected category

www.uptodate.com

Prevalence of anemia in persons 65 years and older in the United States: evidence for a high rate of unexplained anemia

Jack M. Guralnik, Richard S. Eisenstaedt, Luigi Ferrucci, Harvey G. Klein, and Richard C. Woodman

- One of the first population based studies came from NHANES of 4199 community dwelling men and women over 65 years of age in US in early 1990s
- 1/3 due to nutritional deficiencies
  - poor nutrition, malabsorption, blood loss
- 1/3 anemia of chronic inflammation or chronic kidney disease
  - Autoimmune condition, chronic infection, cancer, CHF, chronic low grade inflammation due to aging
- 1/3 unexplained anemia
- Other etiologies: medications, hematologic malignancy, hemolysis, androgen deprivation

Blood 2004; 104: 2263.

NUTRITIONAL DEFICIENCY

- Iron and vitamin B12 are most common
- Folate deficiency is rare and therefore, testing no longer funded in BC (can consider trial of empiric supplementation)
- Reduced intake can be related to poor diet or previous gastric bypass or bowel resection, Helicobacter Pylori infection, celiac disease, atrophic gastritis or inflammatory bowel disease

INVESTIGATION FOR IRON DEFICIENCY

- Ferritin is the most helpful test to assess for iron deficiency.
- Level maybe obscured by concurrent inflammation and checking CRP may help with interpretation
- GI blood loss is a very common reason for iron deficiency. Endoscopy should be considered depending on underlying comorbidities and goals of care

	Normal	IDA	ACD	IDA+ACD
Hb (g/L)	>120 (F), >130 (M)	↓	↓	↓
MCV	80-95	<80	Normal/↓	↓
Ferritin	15-200	<30 (<100)	>100	Normal/↓
Iron	10-30	↓	↓	↓
TIBC		↑	↓	↓
Tsat, %	16-45	↓ (<15-20)	Normal/↓	Normal/↓

TREATMENT FOR IRON DEFICIENCY

- Hepcidin is a hormone peptide synthesized in liver and regulates iron metabolism
- Increased level reduces iron absorption from duodenum
- Hepcidin has a circadian increase over the day. This may affect absorption of supplements taken in the afternoon
- Oral doses of iron supplements have been shown to acutely increase serum hepcidin level, raising concern of lowering absorption of subsequent dose of iron
- Based on these findings, studies have shown alternate day dosing improves iron absorption and there is no benefit of splitting to multiple daily doses.

Moretti D et al. Blood 2015: 126:1981
Stoffel N et al. Lancet Hematology 2017; 4:524.

Are we giving too much iron? Low-dose iron therapy is effective in octogenarians

Ephraim Rimon, MD, Nadya Kagansky, MD, Michael Kagansky, MD, Lora Mechnick, MD, Tony Mashiah, MD, Michael Namir, MD, Shmuel Levy, MD

- 90 hospitalized elderly patient over age 80.

Table 2 Changes in hemoglobin and ferritin values in study participants* during 2 months of iron therapy

Iron dose, daily	Time from first iron dose: Day 0	Time from first iron dose: Day 60	Increase between Day 0 and Day 60 (95% confidence interval)
Hemoglobin (g/dL)	Mean ± SD		
15 mg	10.0 ± 1.1	11.3 ± 0.9†	1.3 (0.7-2.0)
50 mg	10.9 ± 1.0	12.3 ± 0.7†	1.4 (0.8-1.9)
150 mg	10.2 ± 1.3	11.6 ± 0.8†	1.4 (0.9-1.8)
No anemia (15 mg)	13.1 ± 0.9	13.2 ± 0.9	0.2 (0.2-1.5)
Ferritin (ng/mL)			
15 mg	19.8 ± 6.6	60.2 ± 18.5†	40.4 (32.1-48.1)
50 mg	25.1 ± 8.8	61.4 ± 18.2†	36.3 (29.1-42.5)
150 mg	22.2 ± 9.1	66.3 ± 19.5†	44.1 (35.5-50.4)
No anemia (15 mg)	86.5 ± 23.5	90.2 ± 26.7	3.7 (2.1-20.4)

*Thirty participants were assigned to each dose group.
†$P < 0.001$ compared with day 0.

American Journal of Medicine 2005;118:1142

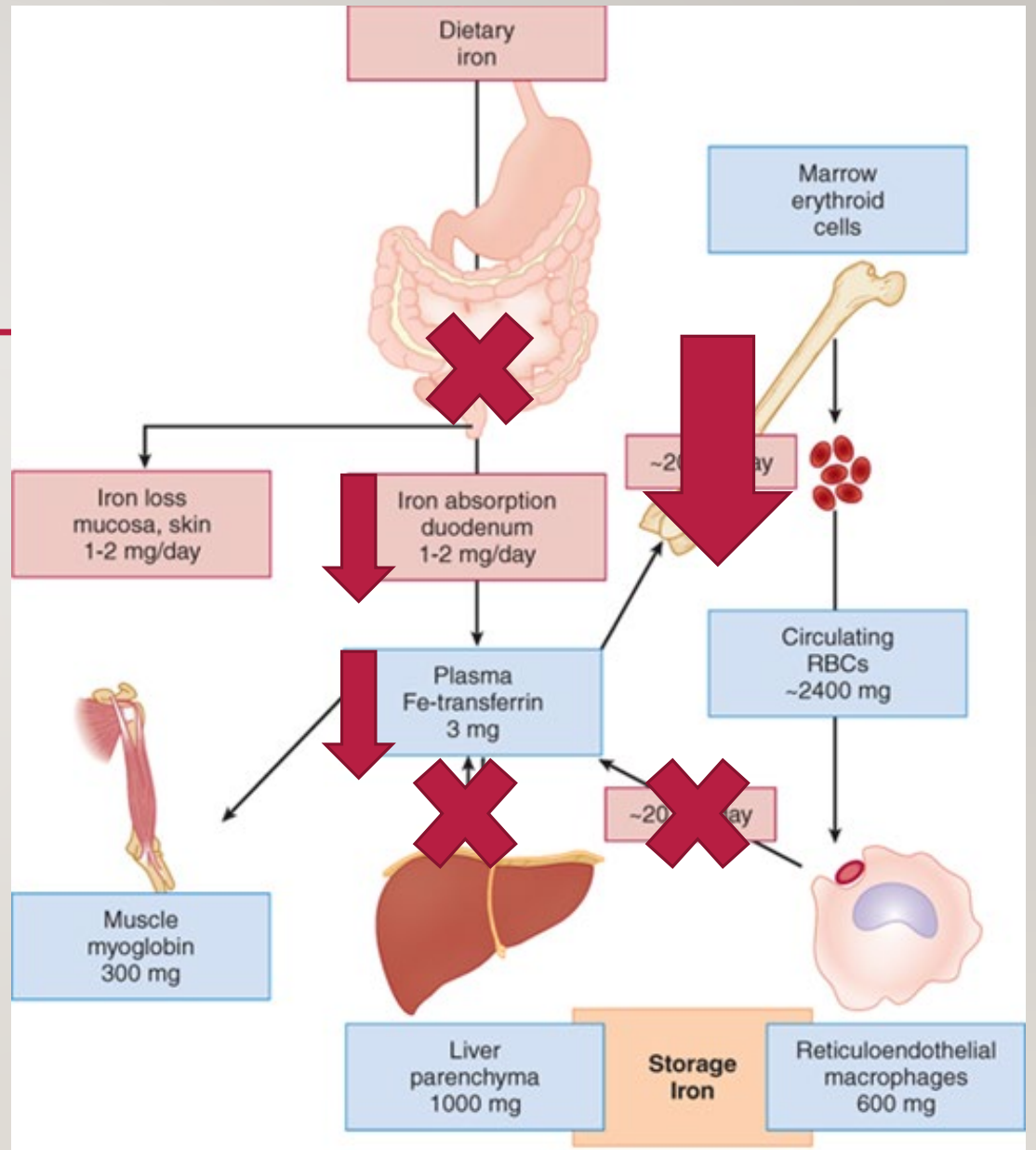
PARENTAL IRON

- Indications:
  - Poor intestinal absorption/active inflammation/poor tolerance to PO iron
  - Needs rapid raise in Hb due to severe anemia
  - Chronic bleeding not responding to PO iron
  - CKD patient on erythropoietin therapy
- Generally well tolerated – risk of headache, muscle and joint aches, rare risk of anaphylaxis.
- In FH, patient would qualify if Ferritin <50 or iron saturation < 20%. Can be ordered by any licensed physician as either iron sucrose and Monoferric (iron isomaltoside)

ANEMIA DUE TO CHRONIC INFLAMMATION

- Hepcidin level increases
  - With inflammation and cancer
  - Higher level of hepcidin reported in older population (?due to age-associated chronic upregulation of proinflammatory cytokines like IL-1, IL-6, and tumor necrosis factor)
- This results in reduced plasma transferrin bound iron. Iron is retained in liver and macrophages and can't get to bone marrow for erythropoiesis
- Treat underlying condition causing inflammation. Erythropoietin therapy in CKD. ?New drug target

Stauder R et al. Blood 2018; 131:505



Source: H. Franklin Bunn, Jon C. Aster: Pathophysiology of Blood Disorders
www.accessmedicine.com
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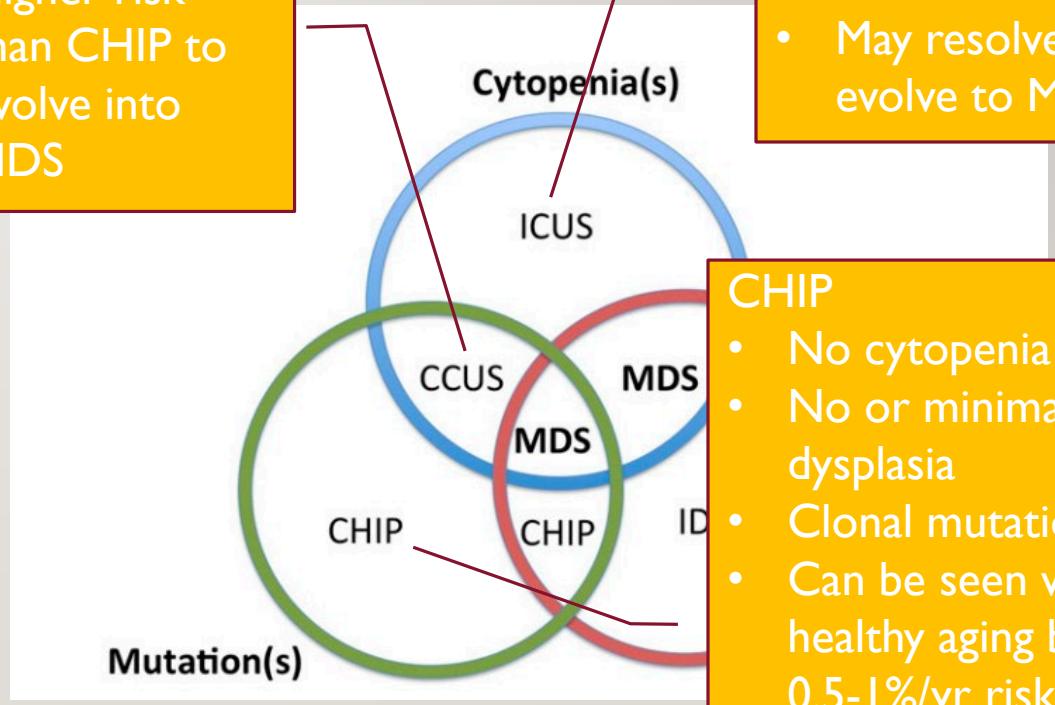
UNEXPLAINED ANEMIA

- Acquired resistance of erythroid cells to EPO is proposed as a potential etiology
- Bone marrow biopsy is required to exclude underlying marrow disorder but may not be pursued if cytopenia mild or patient/family's preference.
- Early changes of MDS in bone marrow maybe subtle making biopsy non-diagnostic.
- Development of NGS created new entities to further classify unexplained cytopenia

CCUS
- Cytopenia
- <10% dysplasia
- Clonal mutation
- Higher risk than CHIP to evolve into MDS

ICUS
- Cytopenia
- < 10% dysplasia
- No clonal mutation
- May resolve or evolve to MDS



CHIP
- No cytopenia
- No or minimal dysplasia
- Clonal mutation
- Can be seen with healthy aging but 0.5-1%/yr risk to become neoplastic

Steensma D. Hematology 2016; 67.

MYELODYSPLASTIC SYNDROME

- Incurable myeloid neoplasm presenting with progressing cytopenia. Risk of progression into acute myeloid leukemia. Median age of diagnosis = 73 years
- Diagnosis based on >10% dysplasia on bone marrow biopsy
- Prognosis depends on degree of cytopenia, percentage of blasts in marrow and cytogenetics finding. New prognostic score also incorporates mutation results on NGS
- Treatment

Low risk MDS	Int – high risk MDS
Transfusion or Erythropoietin therapy	Transfusion support
Lenalidomide (PO chemo) if 5q minus	Azacitadine (SC chemo) 7 days / 28 days
Luspatarcept (SC chemo) if ringed sideroblasts	Decitabine/cedazuridine (PO chemo) 3-5d/28d

WORK UP FOR ANEMIA

- Retic count, LDH, bilirubin, haptoglobin, peripheral smear
- SPEP, UPEP or Serum free light chains
- Ferritin, CRP, Vitamin B12
- Liver and kidney function
- +/- GI work up for iron deficiency – anti-TTG, H pylori, endoscopy
- +/- bone marrow biopsy depending on degree of cytopenia, presence of abnormal finding on peripheral smear and goals of care

CASE 2 BLOODWORK

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CASE 2 MANAGEMENT

- Given mildly symptomatic anemia with active inflammation, she was given IV Fe
- Prednisone increased for arthritis flare
- Started on PPI despite no GI Sx since prednisone dose increased and concern of possible GI blood loss
- Referred to GI for consideration of endoscopy.
- Continue on Apixaban since no overt visible bleed with plan for close monitoring of blood count
- Further bloodwork returned showing no monoclonal protein on SPEP/UPEP, no hemolysis
- Hemoglobin and kidney function improved after completion of IV Fe

QUESTIONS